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Matthew J. Baggott

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Matthew J. Baggott, B.A.

Abstract—Increasing use of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") has been accompanied by concern about acute and possible long-term toxicity. This article discusses acute serious toxicity, chronic toxicity, and common problems associated with Ecstasy use, as well as the implications of these areas for prevention programs targeted at current Ecstasy users. The low incidence of serious adverse events in users creates difficulties for attempts to develop harm reduction recommendations. Many hypothesized risk factors for serious adverse events cannot be confirmed or denied and may not be associated with dramatic elevations in risk. Research on chronic toxicity in users provides strong evidence of neurophysiological changes and suggestive evidence of possible neurocognitive changes. Because these worrisome changes are clinically subtle, users may not be influenced by concerns of neurotoxicity. In contrast, common Ecstasy-related complaints are relatively well documented and have identified risk factors, including factors relating to extent of Ecstasy use (such as "binges"). Common complaints include modest acute and subacute adverse effects, some lasting several days, and problems in life. The apparent willingness of users to modify drug use and other behaviors to decrease these common problems could be used by harm reduction or other prevention programs to encourage users to decrease the extent of Ecstasy use.

Keywords—adverse effects, Ecstasy, harm reduction, MDMA, risk factors

3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") is a substituted phenethylamine that is hypothesized to represent a new class of psychoactive agents called "entactogens." Although MDMA pharmacologically resembles methamphetamine, users frequently report an unusual syndrome of effects that is not associated with psychostimulants, including feelings of sedation, emotional openness, increased closeness to others, and increased sociability (Cami et al. 2000; Vollenweider et al. 1998;

Solowij, Hall & Lee 1992; Shulgin & Nichols 1978). Use of the drug has generally been increasing among adolescents and young adults throughout the 1990s. In the United States in 2000, reported lifetime/previous 30-day use of Ecstasy was 4.3%/1.4% for eighth graders, 7.3%/2.6% for 10th graders, 11.0%/3.6% for 12th graders, and 11.6%/1.9% for young adults (modal ages 19-28) (Johnston, O'Malley & Bachman 2001). Most Ecstasy users appear to be fairly conventional adolescents and young adults except in their tendency to be early risk takers and sensation seekers. The use of Ecstasy by seemingly well-adjusted individuals has led some to suggest that we are seeing a "normalization" of Ecstasy, with the drug becoming an accepted part of social life among the young (Parker, Aldridge & Measham 1998). Jenkins (1999) argues that concern with Ecstasy use is motivated not so much by danger as by social tensions in society. Despite this so-called normalization and the possible social context of concern over Ecstasy, Ecstasy use

has been clearly linked to fatalities and other adverse events. There are also ongoing concerns about long-term neurotoxicity in users. These problems and concerns suggest a need for preventative programs directed at Ecstasy users. Government-sponsored campaigns have emphasized worrisome evidence of neurotoxicity in repeated Ecstasy users. Volunteer-based harm reduction groups have responded to problems in Ecstasy users with informational pamphlets and programs designed to make Ecstasy use less harmful. These efforts are made difficult by the lack of scientific and medical information on this relatively new drug.

This article will discuss problems related to Ecstasy use and the difficulties of making recommendations for reducing these problems. Acute serious toxicity, chronic toxicity, and common problems related to Ecstasy will be discussed. It will be suggested that programs directed at Ecstasy users might more profitably focus on common problems rather than on rare serious adverse events or subtle neurotoxicity. The author is sympathetic to the goals of harm reduction programs, but would like to see programs be guided by the scientific literature and program-specific outcome measures; he is not an authority on drug abuse treatment or public policy, but is familiar with the scientific and medical literature on MDMA and its limitations. One difficulty in discussing and assessing MDMA is that illicit Ecstasy preparations are known to sometimes contain a variety of psychoactive agents other than MDMA (Baggott et al. 2000; Sherlock et al. 1999). For this reason, in this article the term "Ecstasy" is used to refer to illicit preparations of unknown composition and the term "MDMA" is reserved for instances when the presence of MDMA has been confirmed. It should be noted that this article focuses on current Ecstasy users; the initiation of Ecstasy use is an important topic that is beyond the scope of the current discussion. Another limitation of this article is its focus on communications and recommendations to Ecstasy users rather than to nightclub owners and dance event promoters, who have a significant responsibility for maintaining a safe environment for their clients (drug users and nonusers alike).

ACUTE TOXICITY AFTER ECSTASY USE

Illicit use of MDMA has been associated with a number of serious adverse events, including death. Although they are often well publicized, deaths relating to Ecstasy use appear to be fairly rare. It has been estimated that 0.21 and 0.87 Ecstasy-related deaths per 10,000 users occurred annually in England and Scotland, respectively, from 1995 through 1996 (Gore 1999). Similarly, Newcombe and Woods (1999) estimated that there were 40 Ecstasy-related deaths per one million users in England in 1994. Sufficient data are not available in the United States to make an analogous estimate. However, the trickle of cases reported by medical examiners participating in the Drug Abuse

Warning Network (DAWN) suggests the prevalence is lower in the U.S.

Nonfatal adverse events are more common. In 2000, 4,511 Ecstasy-related emergency department (ED) visits were reported in the United States (Office of Applied Studies/Drug Abuse Warning Network 2001). Employing 1999 data from DAWN and the nationwide Monitoring the Future survey of adolescents and young adults, the author has estimated that 2.9 to 3.6 in 10,000 Ecstasy exposures among young adults (18 to 25 years of age) resulted in an ED visit in 1999 (Baggott, Jerome & Stuart 2001). A survey of 329 Australian Ecstasy users provides similar numbers, with respondents reporting the equivalent of at least 11 ED visits in 10,000 Ecstasy exposures (Topp et al. 1999). Although not all problems at raves can be attributed to Ecstasy, data from raves can be seen as providing estimates of upper limits to local rates of Ecstasy-related ED visits. Suy, Gijsenbergh and Baute (1999) participated in first-aid assistance at a large one-night rave near Antwerp, Belgium and reported eight drug-related ED visits per 14,000 attendees. Based on records from first-aid areas at 42 large raves in the Netherlands in 1996 and 1997, Maalsté (1999) estimated that there was approximately one ED visit per 10,000 rave attendees. In a retrospective review of dance-related ED visits to West Lothian (Scotland) hospitals from 1991 and 1992, Freeland (cited in Saunders 1993) estimated that there were at least 2.3 ED visits per 10,000 rave attendees. Given the high prevalence of Ecstasy use at raves, these estimates from raves seem fairly comparable to the 1999 nationwide estimate from the United States.

Several limitations should be noted. Estimates of this sort do not indicate the severity of the adverse events. Published reports of sequential Ecstasy-related cases at EDs suggest many of these cases are modest in severity (Williams et al. 1998). Ecstasy-related adverse events that do not lead to ED visits, such as depressed mood or dental problems, will be undetected by these estimates. Finally, purportedly Ecstasy-related adverse events may not always be due to MDMA, given the varying contents of illicit Ecstasy and frequent polydrug use by users. It should also be noted that the frequencies of ED visits or mortality after Ecstasy use are the result of a complex interaction between pharmacological effects, user characteristics, behavior, and environment. As such, the apparent toxicity of the drug can change as these factors change.

Difficulties Identifying Risk Factors for Acute Toxicity

Serious acute adverse events are sufficiently rare that they are difficult to interpret with certainty. While we can count adverse events at the ED, we cannot easily identify risk factors associated with these adverse events. For example, 47% of Ecstasy-related ED visits in the U.S. in 1999 involved alcohol (Office of Applied Studies/Drug Abuse Warning Network 2001). However, we cannot conclude

from this statistic that alcohol increases risk of adverse event in Ecstasy users without knowing the general prevalence of coadministration of Ecstasy and alcohol. Alcohol is certainly a diuretic and may increase risk of dehydration, but it is not clear how significant this will be in practice. Given these interpretive difficulties, many of the hypothesized risk factors for adverse events after Ecstasy use have not been clearly demonstrated. Instead, hypothesized risk factors are generally derived from clinical impressions of individual cases, knowledge of basic physiology, and animal and in-vitro toxicity studies. The difficulties of identifying and managing Ecstasy-related risks can be amply illustrated by considering, in turn, possible genetic variations in MDMA metabolism and risks of Ecstasy-related hyperthermia.

Hypothesized Risk Factors Relating to MDMA Metabolism

Some hypothesized risk factors are derived from in-vitro laboratory research. It has long been hypothesized that genetic variations in the activity of metabolizing enzymes might influence risk of MDMA toxicity. Cytochrome P450 isozyme 2D6 (CY2D6) was the first enzyme known to be involved in human MDMA metabolism (Tucker et al. 1994). CYP2D6 activity is genetically determined and up to 10% of the Caucasian population has deficient CYP2D6 activity (Gough et al. 1990). It has therefore been suggested that individuals having this autosomal recessive trait might have increased plasma drug concentrations and increased risk of acute adverse response to MDMA.

Pharmacological studies and the lack of evidence from case reports have cast doubt on this theory. Pharmacological studies in humans (de la Torre et al. 2000a, b) and human liver tissue (Kreth et al. 2000) suggest that CYP2D6 plays a relatively modest role in MDMA metabolism. In addition, Kreth and colleagues (2000) reported on an individual with the poor metabolizer trait participating in a clinical study of 3,4-methylenedioxyethylamphetamine (MDE). Formation of the major demethylenated metabolite (presumably via CYP2D6) was approximately 44% that of other volunteers, but maximal MDE plasma concentration was not altered. Published case reports have yet to identify an unexpectedly high proportion of individuals with deficient CYP2D6 activity among individuals with Ecstasy-related problems. O'Donahoe and colleagues (1998) reported that none of seven patients with previous adverse reactions to Ecstasy were homozygous for the poor metabolizer genotype of CYP2D6. Schwab and colleagues (1999) found extensive CYP2D6 activity in three illicit MDMA users who had developed MDMA-related hepatotoxicity. It is impossible to demonstrate that variations in CYP2D6 activity have never played a role in Ecstasy toxicity, but it seems suspicious that this hypothesized role has never been confirmed. To the extent that variation in metabolism is a risk factor, it may be that risk is due to other enzymes participating in MDMA metabolism, which include cytochrome P 450 isozymes 3A4, 2B6, and 1A2 (Kreth et

al. 2000; Maurer et al. 2000; Wu et al. 1997; Tucker et al. 1994).

Hypothesized Risk Factors for Ecstasy-Related Hyperthermia

Most published case reports of adverse events in Ecstasy users describe hyperthermic syndromes, many of them producing death. Risk factors for Ecstasy-related hyperthermia are thought to include high ambient temperature or humidity, dehydration, and exercise. For example, Henry and Rella (2001) write that "it seems apparent that cases of severe hyperthermia and deaths from heatstroke were due mainly to prolonged dancing without rest and without drinking enough liquid to allow for normal temperature control through sweating." Rodent studies indicate that these hypothesized risk factors could be expected to interact with the effects of MDMA on thermoregulation. In these studies, MDMA has been shown to dose-dependently impair thermoregulation, leading to hyperthermia in most settings (Broening, Bowyer & Slikker 1995; Colado & Green 1995; Dafters 1995; Dafters 1994; Gordon et al. 1991). The mechanism of MDMA-induced thermoregulatory impairment is not fully understood, but may include vasoconstriction (slowing heat loss) (Pedersen & Blessing 2001; Gordon et al. 1991) and decreased awareness of discomfort (preventing behavioral thermoregulation, which in humans includes rest, clothes removal, and fluid consumption). MDMA may mask thirst and has been shown to acutely decrease fluid consumption in fluid-deprived rodents (Dafters 1995; Bilsky et al. 1990). Furthermore, ambient temperature has been linked to increased risk of death in overdoses from other stimulants (Marzuk et al. 1998).

Nonetheless, it appears that Ecstasy-related hyperthermia can occur in the absence of these risk factors. In some cases, hyperthermia rapidly develops shortly after consumption of Ecstasy (Demirkiran, Jankovic & Dean 1996; Hall et al. 1996; Brown & Osterloh 1987). Rapidly-developing hyperthermia may have a similar mechanism to the drug-related hyperthermic syndrome, serotonin syndrome. In one published case, a paraplegic individual who had previously used Ecstasy developed hyperthermia after consuming Ecstasy (presence of MDMA was not confirmed) in a pub (Hall et al. 1996). In another case, a woman developed hyperthermia within 15 minutes of consuming one Ecstasy pill (Demirkiran, Jankovic & Dean 1996); MDMA was detected in blood and urine. In a third case, blood concentration of MDMA was very high (6.5 mg/L), suggesting impaired MDMA metabolism or overdose, despite the modest estimated dose of 100-150 mg MDMA (Brown & Osterloh 1987). It is important to emphasize that Ecstasy-related hyperthermia can still occur in MDMA users who avoid hypothesized risk factors. Efforts to educate Ecstasy users about risk factors should not inadvertently suggest that risk of hyperthermia can be entirely eliminated.

It is additionally clear that hypothesized risk factors for Ecstasy-related hyperthermia are fairly common among users and often do not lead to serious adverse events. While exercise is a hypothesized risk factor, millions of individuals dance on Ecstasy each weekend without any obvious problem. Other hypothesized risk factors have a similarly subtle relationship to Ecstasy-related hyperthermia. For example, in a 1993 to 1995 survey of 229 Ecstasy-experienced individuals in Glasgow, Scotland, 34% of current users (N = 201) had consumed no water at the last dance event attended, 75% had consumed some alcohol, and 25% had consumed nine or more units of alcohol (Hammersley, Khan & Ditton 2002). The researchers further noted that users with heavier use of Ecstasy were less likely than lighter users to have drunk water at the last dance event attended. Despite these behaviors, only a small proportion of the sample had ever had problems that required medical attention (although 53% had ever felt unwell on Ecstasy, only four users had ever gotten medical attention for being unwell). Coadministration of Ecstasy and alcohol is common among Ecstasy users. For example, 66.2% of 1,594 Ecstasy users attending dance events in seven European cities reported using alcohol within six hours (before or after) of taking Ecstasy (Tossmann, Boldt & Tensil 2001). In a survey of 122 Scottish drug users in dance event, 28% of respondents reported always mixing drugs and alcohol (Riley et al. 2001). While none of these samples are representative of Ecstasy users in general, they confirm that hypothesized risk factors are common.

An attempt to investigate risk factors at large dance events did not confirm the hypothesized role of temperature and humidity, although the study does illustrate several useful points. Van de Wijngaart and colleagues (1999) interviewed individuals before and after a series of dance events (1,121 participants before the event, of whom 768 returned afterward) and were unable to detect in a regression analysis any role of ambient conditions (including temperature and humidity within the venue) in influencing the incidence of self-reported complaints and illness. Because 353 participants were not interviewed after the event, caution must be used in drawing conclusions from this study. One probably cannot study Ecstasy-related problems that are serious enough to warrant an ED visit without a much larger study. It is also possible that none of the dance events studied achieved dangerous temperature or humidity levels. Nonetheless, the researchers did identify risk factors for common Ecstasy-related complaints, which will be discussed below. They also suggested a potential role for difficult-to-measure risk factors relating to crowding and discomfort of participants. This is interesting because a large literature has established that many amphetamines, including MDMA, have increased lethality when test animals are housed in groups rather than individually (Davis & Borne 1984). Increased lethality appears to be partially due to the stress associated with a novel physical and social environment,

as acclimation reduces the effect of crowding on d-amphetamine lethality (Vargas-Rivera et al. 1990). Of course, self-reported complaints and lethality among Ecstasy users may be unrelated. Still, this study illustrates that fairly large studies may not confirm or deny hypothesized risk factors for serious adverse events, but can investigate risk factors for self-reported complaints.

In the past, harm reduction efforts to decrease Ecstasy-related hyperthermia have led to somewhat mixed results. Ecstasy-related hyperthermia began to occur at dance events with noticeable frequency in England in 1990 (Henry, Jeffreys & Dawling 1992). Public health and harm reduction organizations responded by emphasizing the need to avoid dehydration and overheating. Soon, health-care providers began to encounter hyponatremia in Ecstasy users (Henry 2000; Maxwell, Polkey & Henry 1993). Hyponatremia refers to abnormally low sodium concentration in blood, which can produce neurological symptoms such as nausea, vomiting, agitation, coma and seizures. Ecstasy-related hyponatremia has been fatal in approximately 15% of published case reports (Baggott, Jerome & Stuart 2001). These cases seem to have occurred because user attempts to avoid dehydration interacted with a previously unknown antidiuretic effect of MDMA (Forsling et al. 2002; Henry et al. 1998). For example, between August 1994 and December 1995, 15 cases of Ecstasy-related hyponatremia were identified by the London National Poison Information Service (Henry 2000). Furthermore, it appeared that some users had incorrectly inferred that water was a general antidote to the effects of MDMA. In contrast to most other toxic syndromes seen in Ecstasy users, the majority of cases of Ecstasy-related hyponatremia occurred in females (Baggott, Jerome & Stuart 2001). Premenopausal females generally have elevated risk of death or long-term morbidity from hyponatremia in comparison to males (Ayus & Arieff 1996). Advice to users was rapidly modified and now many harm reduction organizations recommend users drink no more than one pint of water per hour.

Implications of Acute Toxicity for Preventive Efforts

This brief discussion suggests several conclusions. Risk factors for serious Ecstasy-related adverse events are difficult to study and many cannot be confirmed or denied with any confidence. Hypothesized risk factors based on clinical observation need to be interpreted in light of common user behaviors and may only become significant risk factors with extreme severity (e.g., when dehydration sufficient to prevent sweating interacts with drug effects intense enough to mask discomfort). Hypothesized risk factors based on laboratory studies (e.g. CYP2D6 deficiency) or physiological mechanisms (e.g. alcohol and other diuretic consumption) may not be associated with detectable elevations in risk in the real world. One might question whether preventative programs should focus on warning

users about these hypothesized risk factors, which users may know from experience to be unlikely to lead to serious adverse event. Well-intentioned recommendations based on hypothesized risk factors may also have unintended consequences, as was seen with cases of hyponatremia. It is therefore important to evaluate interventions to ensure that users properly understand the information being presented and that recommended behaviors do not have undesirable outcomes. Studying user beliefs and perceptions should be relatively easy, while evaluating the actual outcomes from interventions will prove difficult. Faced with these difficulties and uncertainties, resources might be better spent on decreasing common Ecstasy-related complaints, many of which are related to the extent of Ecstasy use, than trying to prevent rare and poorly understood serious adverse events. If extent of Ecstasy use can be decreased, corresponding decreases in serious adverse events may follow.

CHRONIC TOXICITY IN ECSTASY USERS

Serious acute adverse events and deaths related to Ecstasy use are dramatic. These tragic events have been important in motivating volunteer organizations and governments to respond to drug-related problems. Nonetheless, these events are rare. Some researchers have expressed concern about the possibility of unnoticed toxicity occurring with ongoing Ecstasy use. If ongoing Ecstasy use is associated with significant toxicity, then efforts should be perhaps shifted from addressing rare adverse events to decreasing ongoing Ecstasy-related toxicity. However, aside from serious adverse events, the consequences of repeated MDMA exposure in humans are subtle, and research findings may not be sufficiently conclusive or dramatic to influence Ecstasy users. Research on potential chronic toxicity can be broadly discussed with respect to four overlapping areas: selective serotonergic neurotoxicity in animals; neurophysiological measures of users; serotonergic measures of users; and neurocognitive performance measures of users.

Selective Serotonergic Neurotoxicity in Animals

Much of the concern about long-term toxicity in Ecstasy users originates from animal toxicity studies. Studies in nonhuman animals demonstrate that high or repeated-dose MDMA use can cause apparent swelling and degeneration of a subset of serotonergic axons originating in the dorsal raphe nucleus (O'Hearn et al. 1988). There is no apparent loss of serotonergic cell bodies in this area (Hatzidimitriou, McCann & Ricaurte 1999; Fischer et al. 1995) and axons subsequently regrow from cell bodies, albeit in an altered pattern of innervation in nonhuman primates (Hatzidimitriou, McCann & Ricaurte 1999). Animals exposed to neurotoxic regimens of MDMA have an altered response to a variety of drugs and neurophysiological

changes can be detected, but behavioral correlates of serotonergic changes have proven subtle. In one study, rats exposed to a neurotoxic MDMA regimen showed reductions in diurnal and nocturnal locomotor activity at one to two weeks after drug exposure (Wallace, Gudelsky & Vorhees 2001). Two studies indicate that these animals have increased risk of hyperthermia when placed in warm settings at up to 14 weeks after drug exposure (Mechan et al. 2001; Hatzidimitriou, McCann & Ricaurte 1999; Dafters & Lynch 1998). Neurocognitive performance has proven to be surprisingly robust, and many studies have failed to detect alterations in these areas persisting more than a few days after MDMA exposure. Nonetheless, drug-free neurocognitive performance was reported as altered in two studies (Broening et al. 2001; Marston et al. 1999), one of which administered MDMA to neonatal rats that were argued to be developmentally similar to third-trimester human fetuses (Broening et al. 2001). There have been conflicting reports about alterations in anxiety in rats exposed to neurotoxic MDMA regimens. In one study, anxiety-related behavior was altered in rats exposed to a presumably neurotoxic MDMA regimen, suggesting a long-term decrease in anxiety (Mechan et al. 2002). In a second study, an apparent long-term increase in anxiety was seen in rats exposed to either a neurotoxic or a presumably non-neurotoxic MDMA regimen (Morley et al. 2001).

Neurophysiological Measures in Ecstasy Users

Studies of illicit Ecstasy users have found strong evidence of neurophysiological changes. There is evidence that at least some MDMA exposures in humans can produce cerebrovascular alterations lasting at least several weeks (Chang et al. 2000; Reneman et al. 2000a, b). Taken together, the studies suggest that MDMA exposure may cause a subacute down-regulation in both 5-HT_{2A} receptor density and cerebral blood flow lasting several weeks. A subsequent increase in 5-HT_{2A} receptor density and vasodilatation may occur in some individuals, possibly as a result of serotonergic neurotoxicity. Two studies have used 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography to detect modest decreases in glucose metabolism in some brain regions of Ecstasy users (Buchert et al. 2001; Obrocki et al. 1999). Three studies using proton magnetic resonance spectroscopy measures of cerebral metabolites have detected different changes in illicit users, with one study suggesting possible neuronal dysfunction (Reneman et al. 2002), a small study finding no changes (Obergriesser et al. 2001), and the other study reporting possible glial activation (Chang et al. 1999). Electroencephalography has detected apparent alterations in Ecstasy users in four studies (Croft et al. 2001a; Gamma et al. 2000; Tuchtenhagen et al. 2000; Dafters et al. 1999). Evidence that these apparent alterations are related to Ecstasy exposure comes from correlations between Ecstasy exposure and measures such as brain myo-inositol increases

(Chang et al. 1999), brain N-acetylaspartate decreases (Reneman et al. 2002) and EEG alterations (Croft et al. 2001a; Dafters et al. 1999). A primary difficulty in interpreting these studies is that we do not really know the implications of these apparent neurofunctional differences. Few neurophysiological measures have been validated as sensitive to long-term effects of MDMA-like drugs in animals (McBean et al. 1990; Sharkey, McBean & Kelly 1991) and none are selective for serotonergic neurotoxicity.

Serotonergic Measures in Ecstasy Users

Do the neurophysiological alterations in illicit users suggest that serotonergic neurotoxicity has taken place? This is a possibility supported by studies attempting to measure serotonergic alterations. Several studies have shown differences in measures of serotonergic functioning between users and nonusers. Three groups have reported decreased cortical SERT binding in Ecstasy users (Reneman et al. 2001a, b; Semple et al. 1999; McCann et al. 1998), although there is some question about the specificity of the measurement technique (Kish 2002; Buck et al. 2000; Heinz & Jones 2000; Kuikka & Ahonen 1999), and evidence of reversibility from two of the groups (Reneman et al. 2001a, b; Semple et al. 1999) increases doubts as to whether axonal loss is being measured. Three of four studies have found CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid to be lower in users than nonusers (decreased in McCann et al. 1999a; McCann et al. 1994; Ricaurte et al. 1990; unchanged in Peroutka, Pascoe & Faull 1987). Two studies have used electroencephalography to measure a putative indicator of serotonergic functioning (intensity dependence of auditory evoked potentials) and found possible serotonergic changes in Ecstasy users but not cannabis users (Croft et al. 2001a; Tuchtenhager et al. 2000). Measuring the amount of hormone released in response to a serotonergic drug has been used to test for changes in the serotonergic system. This technique has uncovered statistically significant differences between users and nonusers in four of six studies (differences were detected in Verkes et al. 2001; Gerra et al. 2000; McCann et al. 1999; Gerra et al. 1998; no significant differences were found in McCann et al. 1994; Price et al. 1989). Together, these studies provide evidence of serotonergic alterations in Ecstasy users. However, because apparent serotonergic alterations may have causes other than MDMA-induced loss of axons, these findings are not conclusive evidence of serotonergic neurotoxicity. Prospective studies using well-validated measures of serotonergic functioning are needed.

For now, the strongest argument that serotonergic neurotoxicity occurs in some Ecstasy users may come from comparison of MDMA exposure levels between animals and humans. McCann and Ricaurte (2001) have argued that interspecies scaling can be used to accurately predict the neurotoxic dose in humans. However, McCann and Ricaurte employed a scaling formula appropriate for drugs that are primarily physically excreted rather than metabolized, have no toxicologically-relevant metabolites, and have linear pharmacokinetics (Mordenti & Chappell 1989). Because MDMA has nonlinear pharmacokinetics (de la Torre et al. 2000a, b) and metabolites that may participate in neurotoxicity (Monks et al. 1999; Ricaurte et al. 1985), the accuracy of this formula is questionable. It is true that the same MDMA dose (in mg/kg) produces a longer drug exposure in humans than in rats, which may make humans more susceptible than rats to some types of toxicity. Furthermore, interspecies scaling is not required to demonstrate that many users ingest Ecstasy doses greater than 5.0 mg/kg MDMA, which produces neurotoxicity in squirrel monkeys (Ricaurte et al. 1988).

Neurocognitive Measures in Ecstasy Users

A growing number of studies suggest that Ecstasy users may experience statistically significant but clinically subtle decreases in neurocognitive performance. These alterations have been most consistently documented using tests of verbal memory and, to a lesser extent, tests of executive functioning and working memory (Fox, Parrott & Turner 2001; Gouzoulis-Mayfrank et al. 2000; Reneman et al. 2000a; Wareing, Fisk & Murphy 2000; Morgan 1999; Bolla, McCann & Ricaurte 1998). There is some question whether these apparent changes can be attributed to MDMA exposure, particularly because most Ecstasy users in the studies also use cannabis, which produces long-lasting residual effects on memory (Pope & Yurgelun-Todd 1996). When an attempt is made to adequately control for use of other drugs, lower neurocognitive performance is not always detected (Croft et al. 2001b), and Parrott (2001) has suggested that a publication bias may be preventing publication of similar nonsignificant findings. Considered together, studies of illicit users associate Ecstasy use with lower neurocognitive performance, but have not yet clearly established that MDMA actually causes lower neurocognitive performance. As discussed above, studies in MDMA-exposed animals support the possibility that MDMA can decrease neurocognitive performance. Until recently, there was little evidence that Ecstasy users perceived any decrease in their neurocognitive abilities (Rodgers 2000; McCann et al. 1999b). It is difficult to say to what extent recent reports of self-reported neurocognitive changes (Fox, Parrott & Turner 2001; Heffernan et al. 2001; Rodgers et al. 2001) were influenced by publicity surrounding earlier findings.

Implications of Possible Chronic Toxicity for Preventative Efforts

Studies of illicit Ecstasy users provide strong evidence that repeated MDMA exposure has detectable effects on the brains of users and raises concerns about the possibility of serotonergic neurotoxicity. What are the implications of this for Ecstasy users? MDMA-induced serotonergic

neurotoxicity in animals is dose-dependent, with a threshold exposure probably being required for loss of axons. Individual doses of MDMA that are not neurotoxic may become neurotoxic if repeated within several hours (O'Shea et al. 1998; Battaglia, Yeh & De Souza 1988). This suggests that dose should be minimized and repeated dosing avoided. Coadministration of hallucinogens increases neurotoxicity (Gudelsky, Yamamoto & Nash 1994). Theories that dopamine release contributes to neurotoxicity (Sprague, Everman & Nichols 1998) suggest that drugs that increase extracellular dopamine levels, such as cocaine or amphetamines, may increase neurotoxicity. This suggests that specific polydrug combinations should be avoided. Different rat strains vary widely in their sensitivity to MDMA-induced neurotoxicity (O'Shea et al. 1998; Logan et al. 1988). This implies that there may be large inter-individual differences in vulnerability to neurotoxicity in humans.

There are other promising potential preventative measures that cannot yet be recommended. A number of rodent studies suggest that neuroprotective agents or cool environments could theoretically be used to decrease risk of neurotoxicity. For example, rodent studies suggest that antioxidants, taken before and during MDMA intoxication, can decrease the extent of serotonergic neurotoxicity (Shankaran, Yamamoto & Gudelsky 2001; Aguirre et al. 1999). Selective serotonin reuptake inhibitors (SSRIs), administered three to four hours after MDMA, may decrease neurotoxicity (Shankaran, Yamamoto & Gudelsky 1999; Schmidt 1987) and many of the subsequent subacute effects of MDMA. Serotonergic neurotoxicity in rats correlates with extent of drug-induced hyperthermia, and preventing hyperthermia reduces neurotoxicity (Malberg & Seiden 1998; Broening, Bowyer & Slikker 1995; Colado & Green 1995; Colado, Murray & Green 1993). These matters have been discussed on harm reduction web sites and in dance and drug culture magazines. As a result, a minority of Ecstasy users appears to be taking antioxidants and, less often, SSRIs in the hope of avoiding neurotoxicity.

There would be a number of serious concerns about recommending these potentially neuroprotective agents or practices to users. First, we do not yet know to what extent Ecstasy-related problems are due to selective serotonergic neurotoxicity as opposed to residual drug effects or other types of toxicity. After all, psychostimulants that are not selective neurotoxins are associated with many problems, including neurocognitive (Bolla, Rothman & Cadet 1999) and cerebrovascular (Herning et al. 1999) changes, in illicit users. In one study, rats intraperitoneally injected with 5 mg/kg MDMA twice (at a 24-hour interval) were reported to have long-term alterations in anxiety-related behavior (Morley et al. 2001), even though that regimen is not expected to produce serotonergic neurotoxicity. In another study, there was no apparent relationship between serotonergic neurotoxicity and memory alterations in neonatal rats

exposed to MDMA (Broening et al. 2001). Thus, reducing serotonergic changes may not reduce Ecstasy-related problems. Second, we do to not know what doses, routes of administration, and timing of administration would be protective in humans. Most of the compounds that have been protective in rats have been injected and it is not clear if humans can achieve comparable brain concentrations of these compounds using oral administration. For example, ascorbic acid (vitamin C) has nonlinear pharmacokinetics in humans, with decreased absorption and increased clearance after high doses (Blanchard, Tozer & Rowland 1997; Graumlich et al. 1997). As a result, oral administration of ascorbic acid may not achieve neuroprotective concentrations. Third, some potential interventions might increase risks of other Ecstasy-related problems. For example, SSRIs are among the few potentially neuroprotective agents known to achieve significant brain concentrations after oral dosing. However, there are theoretical concerns that coadministration of SSRIs and MDMA could competitively inhibit metabolism of both compounds, leading to increased risk of toxicity. Although citalopram and MDMA have been coadministered in clinical studies without adverse incident (Liechti & Vollenweider 2000) and anecdotal reports from users describe similar coadministration, one published case report suggests a possible adverse interaction between citalopram and Ecstasy (the presence of MDMA was not confirmed; see Lauerma, Wuorela & Halme 1998). Fourth, there may be significant species differences between rodents and primates, including humans. The protective effect of cooling MDMA-exposed animals has never been investigated in nonhuman primates and parallel studies with methamphetamine suggest that preventing hyperthermia protects rodents (Miller & O'Callaghan 1994) but does not protect primates (Melega et al. 1998) from methamphetamine-induced neurotoxicity. Finally, one might be concerned that the perception of neuroprotection could increase Ecstasy use (and related problems) by established users and nonusers. Until these concerns are more adequately addressed, potentially neuroprotective interventions should probably be considered experimental and not actively recommended to users.

Information on potential neurotoxicity could, and perhaps should, be used to discourage Ecstasy use. It is unclear whether current users will be influenced by these efforts. Certainly Ecstasy users are aware of this issue. For example, in a 1994 study of 21 Scottish Ecstasy users, this was the area about which participants wanted the most information (Hammersley et al. 1999). Similarly, Measham, Aldridge and Parker (2001) found that 79.5% of dance drug users in their sample were concerned about the potential effects of drug use on their health and future well-being. One-third indicated that uncertainty about effects on their future health and well-being affected them. It might be argued that evidence of chronic toxicity in Ecstasy users is not yet conclusive and that overreliance on this evidence

in prevention messages risks being perceived as either unrealistically alarmist or too ambiguous and speculative. User attitudes about neurotoxicity and the potential influence of neurotoxicity concerns on future Ecstasy use are empirical matters that deserve investigation.

COMMON ECSTASY-RELATED PROBLEMS

There are number of physical and psychological complaints that have been consistently associated with Ecstasy use. These complaints are modest in severity compared to rare serious adverse events and the direst predictions of the consequences of serotonergic neurotoxicity. Still, they are potentially important in at least two ways. First, these complaints are sufficiently common that they can be studied in large surveys and statistical analyses can determine their relationships to demographic and drug use variables. In short, protective and risk factors for common Ecstasy-related complaints can be identified. Second, there is evidence that users attempt to modify their behavior to manage or avoid Ecstasy-related problems. This may prove useful for designing empirically-grounded preventative measures targeted at current users. This section will primarily draw on several relatively large surveys of Ecstasy users (Measham, Aldridge & Parker 2001; Hammersley et al. 1999; Topp et al. 1999). The users in these studies are not representative of users in general and probably overrepresent individuals more closely involved with dance music subcultures and more likely to report Ecstasy-related problems.

Acute Complaints

Commonly reported acute psychological "side effects" of Ecstasy include increased anxiety, confusion, difficulty concentrating, agitation, depressed mood, feeling distant from others, and feelings of dissociation; jaw clenching, sweating, nausea, dry mouth, insomnia, loss of appetite, tremor, headaches, and blurred vision are frequently reported adverse physiological effects of Ecstasy (Liechti, Gamma & Vollenweider 2001; Schifano et al. 1998; Curran & Travill 1997; Davison & Parrott 1997; Parrott & Stuart 1997; Cohen 1995; Solowij, Hall & Lee 1992; Peroutka, Newman & Harris 1988; Siegel 1986).

Subacute Complaints

Some Ecstasy-related complaints begin after the drug intoxication has resolved and may last up to several days. Commonly reported subacute symptoms in surveys of Ecstasy users include depressed mood, insomnia, irritability, anxiety, decreased alertness, fatigue, decreased appetite, muscle aches, and tight jaw (Measham, Aldridge & Parker 2001; Curran 2000; Topp et al. 1999; van de Wijngaart et al. 1999; Parrott & Lasky 1998; Curran & Travill 1997; Davison & Parrott 1997; Liester et al. 1992; Solowij, Hall & Lee 1992;). In clinical studies administering MDMA to healthy volunteers, some volunteers have reported similar

symptoms, such as fatigue, mild anxiety, or depressed mood up to several days after MDMA use (Baggott, Jerome & Stuart 2001; Liechti, Gamma & Vollenweider 2001). Although they are modest in clinical studies, the severity of these symptoms may approach those of major depression in some illicit users (Curran & Travill 1997). User lore explains these symptoms as the results of acute serotonin depletion, a phenomenon documented in rat studies. However, acute serotonin depletion does not occur after every behaviorally active MDMA dose in rats and is primarily associated with neurotoxic doses (Schmidt, Wu & Lovenberg 1986). Given the time course and symptoms of subacute Ecstasy effects, it seems more likely that symptoms are due to an imbalance between monoaminergic neurotransmitter release and postsynaptic receptor number or sensitivity.

Impact of Ecstasy Use on Life

Subacute symptoms are generally of sufficient duration as to potentially overlap with work, study, and career commitments. In the survey of 317 British dance drug users by Measham, Aldridge and Parker (2001), 41.2% of respondents felt that their drug use or recovery period adversely affected their work or study (5.4% felt drug use improved work performance), generally due to fatigue, decreased performance/quality of work, absence or lateness, decreased or labile mood, and lack of concentration. Topp and colleagues (1999) found that 42% of 329 Australian Ecstasy users had reportedly experienced occupational problems in the preceding six months that were related to Ecstasy use. These problems, which were more common in females than males, most commonly involved trouble concentrating, reduced performance, or feeling unmotivated. Forty percent reported relationship problems and 38% reported relationship problems related to Ecstasy use in the preceding six months. Although these surveys are not representative of Ecstasy users in general, they indicate that many Ecstasy users are aware of Ecstasy-related problems in their lives.

MDMA Dependence

Continuing use of a drug despite experiencing problems with health, work, or relationships is a criterion of drug dependence. Until recently, Ecstasy dependence was relatively undocumented (Jansen 1999) because very few individuals seek treatment for substance abuse with Ecstasy as a primary problem. Nonetheless, there is growing recognition that some users can be classified as dependent on Ecstasy. Two percent of users surveyed by Solowij, Hall and Lee (1992) reported having felt dependent on Ecstasy at some time. In a survey of 329 Australian users, 25% of participants wished to reduce Ecstasy consumption, with 16% of this subgroup reporting that feeling dependent on Ecstasy was a motivation to decrease consumption (Topp et al. 1999). Analyzing results of a survey mailed to

readers of a dance music magazine, Winstock, Griffiths and Stewart (2001) reported that over 15% of 1,151 respondents had scores for Ecstasy use on the Severity of Dependence Scale that would indicate problematic use of amphetamine (Topp & Mattick 1997). Among the criteria of dependence documented in this survey, 58% of respondents reported the development of tolerance to Ecstasy, 55% reported continuing use of Ecstasy despite experiencing problems with health, work, or relationships, 36% reported loss of interest in activities or friends not connected with Ecstasy, and 25% reported difficulty controlling the amount of Ecstasy they used. In order to investigate whether Ecstasy use could lead to dependence, Cottler and colleagues (2001) interviewed 52 individuals who reported using Ecstasy more than five times. Forty three percent were diagnosed as dependent, with frequently reported criteria including: continued use despite knowledge of problems from it (63% of users); withdrawal or using to avoid withdrawal (59%); spending a lot of time obtaining or using Ecstasy (39%); and tolerance to Ecstasy (35%).

Interestingly, only 8% of respondents in the Cottler and colleagues study reported a persistent desire to cut down or control Ecstasy use. This is consistent with the apparently low rate of Ecstasy users seeking treatment for substance abuse problems. For example, treatment data from the Netherlands in 1999 indicate that 0.63% of estimated recent Ecstasy users sought outpatient addiction treatment for Ecstasy use and 1.37% sought treatment for another drug but had Ecstasy use as a secondary problem (Trimbos Institute 2000). As a comparison, 6.23% and 4.31% of estimated recent users of amphetamines sought outpatient addiction treatment with amphetamines as a primary or secondary problem, respectively. However, this lower rate of treatment-seeking by Ecstasy users may not be due to an actual difference in proportions of dependent users. Moreover, only a modest proportion of dependent individuals can be expected to seek treatment.

These samples are not representative of Ecstasy users in general and do not indicate what proportion of Ecstasy users are dependent. There appears to be only one published study documenting Ecstasy dependence in a representative sample. Von Sydow and colleagues (2001) studied changes in drug use patterns as part of a four-year prospective longitudinal study of a representative sample of 2,446 German youth (see also Schuster et al. 1998 for an earlier report on the same sample). Ecstasy use was documented in the categories of "stimulants and related substances" and "hallucinogens" apparently due to concerns about distinguishing between Ecstasy-like compounds. At baseline assessment (at ages 14 to 17), 10.4% of individuals who had ever used Ecstasy and related drugs had, at some point, fulfilled DSM-IV criteria for abuse (without dependence) and 8.3% had done so for dependence. The cumulative lifetime incidence at follow-up (ages 18 to 24) was 11.0% of Ecstasy-experienced individuals for abuse

and 6.6% for dependence. Interestingly, there was a general tendency to reduce use of Ecstasy and related drugs by both problem users and users without disorders. About 80% of those initially diagnosed with abuse had improved at follow-up, mostly by becoming nonusers (67.2%) or users without disorder (14.9%). Of those users with initial dependence, 6.7% remained dependent and 7.5% had transitioned to abuse (without dependence). The remainder of formerly dependent users had quit (50.0%) or were using without disorder (35.8%). This study indicates that the incidence of Ecstasy dependence is modest and that the duration of Ecstasy abuse or dependence is limited for many problem users.

User Attempts to Alter Ecstasy Use to Cope with Side Effects and Adverse Experiences

Several surveys indicate that some Ecstasy users attempt to modify their drug use, often in response to negative experiences. Measham, Aldridge and Parker (2001) found that 12.9% of 317 British dance drug users had changed the quantity of dance drugs they used in order to avoid negative drug-related effects. Nine percent had changed their frequency of drug use for the same reason. In a survey of 747 users from nine European cities, 54% of respondents indicated that they had considered giving up Ecstasy use at one time, although reasons were not recorded (Calafat et al. 2001). Hammersley, Khan, and Ditton (2002) found that 41% of 209 Scottish Ecstasy-experienced individuals had reportedly given up Ecstasy at one time or another. The most frequently cited reasons for quitting were: bad side effects (39%); bad comedown (16%); changed life circumstances (12%); loss of interest (10%); and low quality of available Ecstasy (10%). Topp and colleagues (1999) found that 46% of 329 Australian Ecstasy users had attempted to modify their Ecstasy use without formal assistance and 25% wished to reduce Ecstasy consumption. Motivations given included financial difficulties (57% of users), physical health problems (45%), occupational problems (37%), desire to improve quality of life (28%), relationship problems (17%), and feeling dependent on Ecstasy (16%). Multiple logistic regression determined that desire to reduce Ecstasy use in this sample was independently associated with financial problems (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.2-3.9), relationship problems (OR 2.2, CI 1.2-3.9), more psychological side effects (OR 1.2, CI 1.1-1.4), and more frequent use (OR 1.1, CI 1.0-1.2). This model correctly classified 80% of the sample. Winstock, Griffiths and Stewart (2001) found that 53% of 1,106 respondents had reportedly decreased frequency of Ecstasy use of the last year and 9% had stopped using altogether. Twenty-four percent reported using smaller amounts of Ecstasy than in the past. Among the factors potentially influencing Ecstasy use, having a bad experience on Ecstasy influenced 22% of 1,078 respondents to use less Ecstasy (57% reported their use was not affected) and feeling depressed after

Ecstasy use influenced 27% of respondents to use less Ecstasy (60% were reportedly uninfluenced). Keeping in mind that these samples are not representative of all Ecstasy users, there appears to be a significant proportion of Ecstasy users who have decreased or would like to decrease Ecstasy use. In many cases, this desire appears to be related to negative drug-related experiences. This is interesting because it sometimes has been difficult to detect an influence of negative experiences on subsequent drug use (Boys et al. 1999).

Other User Attempts to Cope with Side Effects and Adverse Experiences

In addition to modify their drug use, users employ a variety of other strategies in an attempt to minimize Ecstasy-related problems (Hansen, Maycock & Lower 2001; Measham, Aldridge & Parker 2001; Akram & Galt 1999). Attempts to cope with Ecstasy-related problems fall into several categories. Some involve a general healthy lifestyle (e.g., eating well, exercising). Others are behaviors carried out during drug use that attempt to prevent problems (e.g., pill testing, drinking well, taking breaks from dancing). Others are probably attempts to manage adverse symptoms after they appear (e.g., with illicit, over-the-counter or prescribed medication while coming down from Ecstasy). Finally, some are specific attempts to avoid Ecstasy-induced serotonergic neurotoxicity (e.g., antioxidants taken with Ecstasy, SSRIs taken after Ecstasy). The range of strategies is illustrated by Measham, Aldridge and Parker (2001) who asked 317 British dance drug users how they avoided negative effects associated with drug use. Only 22.9% did not have some strategy for avoiding toxicity. Aside from modifying dance drug use, reported strategies were: drinking well (23.9%); eating well (20%); getting sleep (12.6%); taking other illicit drugs (11.3%); getting support from others (9.7%); taking care over one's frame of mind (9.0%); relax/rest/"chill out" (9.0%); taking vitamins (7.7%); taking over-the-counter or prescribed medication (4.8%); exercise (3.2%); taking care over one's environment (1.6%); and quality control of drugs consumed (1.0%). Although only 1% of respondents listed quality control, Ecstasy pill testing has become a highly visible aspect of a number of preventative organizations. Buying Ecstasy pills from friends or consistent sources (Calafat et al. 2001; Hansen, Maycock & Lower 2001; Measham, Aldridge & Parker 2001; van de Wijngaart et al. 1999) and having pills tested are two important strategies that users employ to ensure "good quality" Ecstasy. Pill testing is discussed below.

While many users report employing these kinds of strategies, some are inconsistent in their application of risk reduction strategies. For example, in several samples, only a minority of users who perceive risks from pill adulteration consistently employs pill testing (Calafat et al. 2001; Hansen, Maycock & Lower 2001; van de Wijngaart et al. 1999). It has been suggested that, as users become more

experienced, they become more comfortable with Ecstasy-related risks and become less consistent in their use of risk reduction strategies (Hansen, Maycock & Lower 2001). It is common for individuals to underestimate familiar risks. Still, one might wonder whether this is also partially because experienced users do not see evidence of increased risks or harm from commonly hypothesized risk factors for Ecstasy-related serious adverse events.

Pill Testing

Quality control of Ecstasy has become an important issue for Ecstasy users. In a European survey, 801 Ecstasy users and 826 nonusers were asked to choose one response from a list of reasons why Ecstasy could cause problems (Calafat et al. 1999). The two reasons most commonly endorsed by users were "unforeseeable effects" (about 27% of users) and "pill adulteration" (about 22%). In contrast, nonusers endorsed "pill adulteration" as a cause of problems about half as often as users (about 12%) and endorsed "unforeseeable effects" more often (about 40%). The concern about pill adulteration among users is due to well-publicized deaths caused by amphetamine-like compounds sold as Ecstasy, such as paramethoxyamphetamine (PMA), paramethoxymethamphetamine (PMMA), and 4-methylthioamphetamine (4-MTA) (De Letter et al. 2001; Decaestecker et al. 2001; Kraner et al. 2001; Ling et al. 2001; Martin 2001; Byard et al. 1998; Felgate et al. 1998). In response to these deaths, some advocates of Ecstasy and volunteer organizations that have emphasized that "the most likely danger from taking Ecstasy is consuming something else instead" (Saunders 1993; see also Sferios 2001). There are few published data that facilitate a comparison of MDMA to these other compounds (European Monitoring Centre for Drugs and Drug Addiction 2001b, 1999). In an analysis of ED cases, 22 cases known to involve PMA did appear to be more severe than 61 other Ecstasy-related ED cases (Ling et al. 2001). A study using rats suggested that PMA may produce a greater degree of hyperthermia in warm ambient temperature conditions than MDMA (compared on a mg/kg basis; see Daws et al. 2000). In addition, adverse events relating to these three adulterants seem to occur shortly after their introduction into geographical areas, suggesting a high rate of adverse event with typical conditions of Ecstasy use. While these data do suggest increased risk from PMA and the other compounds compared to MDMA, confident comparisons are not yet possible.

Motivated by ethical considerations and a desire to reduce drug-related harms, a number of organizations have initiated programs that test Ecstasy pills submitted by users. In addition to screening out compounds that may be more dangerous than MDMA, pill testing provides up-to-date information on what Ecstasy users are actually consuming and brings users into contact with public health organizations. Some programs test pills in batches at

analytical chemistry laboratories, while others perform on-site tests at dance events. Although popular with users, these programs have proven controversial for a number of reasons. Questions have been raised about the validity and reliability of some of the techniques employed (Winstock, Wolff & Ramsey 2001). One technique commonly employed in on-site testing is the Marquis reagent, a sulfuric acid and formaldehyde solution that changes color in chemical reaction with certain functional groups in compounds. This technique is universally acknowledged as imperfect. However, a number of more sophisticated analytical techniques, such as high-pressure liquid chromatography (Meyer 2000) or near-infrared spectroscopy (Sondermann & Kovar 1999), could replace the Marquis test in on-site testing if sufficient funding and official cooperation were available to testing programs.

More fundamental concerns about pill testing involve the unknown impact of pill testing on the use of drugs and the incidence of adverse events in Ecstasy users. It has been suggested that some users may increase drug consumption if they are reassured that MDMA is present in a pill (Winstock, Wolff & Ramsey 2001). Although at least one survey suggests interventions affecting perceptions of pill quality may increase Ecstasy use (Winstock, Griffiths & Stewart 2001), there appears to be no published research on actual user behavior. Concerns about pill testing increasing MDMA consumption and related risks are not likely to go away, and organizations engaged in pill testing would probably be wise to attempt to evaluate the impact of their programs. The European Monitoring Centre for Drugs and Drug Addiction report on pill testing provides sympathetic advice on conducting evaluations (European Monitoring Centre for Drugs and Drug Addiction 2001a).

Risk and Protective Factors for Common Ecstasy-Related Complaints

Several surveys and studies have investigated relationships between Ecstasy-related problems and demographic and drug use variables. Results of these analyses are shown in Table 1. "Bingeing," sometimes called "boosting" or "bumping," refers to repeated administration of Ecstasy to extend drug effects, often done to facilitate extended participation in dance events. While Topp and colleagues (1999) used the term only for periods of drug use without sleep lasting more than 48 hours, other researchers cited did not formally define the term. Not all of the variables in Table 1 can be expected to play a causal role in Ecstasy-related complaints. Some may be consequences of Ecstasy-related complaints. Others may be false correlates that are associated with problematic drug use or lack of health consciousness. For example, more psychological complaints are reported by individuals typically using a greater number of drugs when recovering from Ecstasy. However, these psychological symptoms are more likely a cause then an effect of using drugs to aid recovery.

Determining the direction of causality in these correlations is not always easy, but clinical studies administering MDMA to healthy volunteers support the apparent roles of dose and gender in contributing to Ecstasy-related problems.

Liechti, Gamma and Vollenweider (2001), in an analysis of clinical studies from their group, confirmed that some adverse side effects are gender- and dose-dependent. There were significant differences in intensity of drug effects between men and women. In general, women reported more intense psychological effects than men, while men showed greater increases in physiological measures, particularly systolic blood pressure. Females reported more acute and subacute complaints after Ecstasy use than men. Because the drug was administered with reference to body weight (mg/kg), these gender differences cannot be attributed to the fact that men are generally larger than women. While body size may play a role in gender differences in illicit users, it appears that there are also pharmacokinetic and/or pharmacodynamic differences between genders. Over the dose range studied (70 to 150 mg, administered as 1.35-1.8 mg/kg MDMA), increasing dose was correlated both with greater self-reported hallucinogen-like perceptual effects (particularly in women) and with greater self-reported dysphoric states in women only. On the other hand, increasing dose was not associated with increases in measures of desired drug effects, such as the positively-experienced "oceanic boundlessness" scale. Although hallucinogen-like perceptual effects may well be desirable for users, these findings are consistent with studies of illicit users that suggest increasing dose may lead to a greater proportion of adverse effects compared to desired effects, particularly in women.

Being younger and initiating drug use at a younger age are also associated with increased problems. Greater experience with Ecstasy or amphetamine use appears to be associated with decreased problems (van de Wijngaart et al. 1999) and age is correlated with number of harm reduction strategies employed (Measham, Aldridge & Parker 2001). Still, the association between youth and increased problems probably cannot be wholly explained by inexperience. It appears that the older dance drug users are when they begin using drugs, the less likely they are to experience problems. This suggests that primary prevention programs that merely delay the onset of Ecstasy use may still be useful.

Implications of Common Ecstasy-Related Problems for Preventative Measures

A number of Ecstasy-related problems are common among users, including acute complaints during Ecstasy use, subacute complaints lasting several days after drug use, and life problems related to drug use. These common Ecstasy-related problems may be a more useful focus for harm reduction and other programs directed at Ecstasy users than rare serious adverse events or possible chronic

TABLE 1
Risk Factors for Common Ecstasy-Related Problems

Risk Factor	Associated Event	Statistical Test	Reference
Ecstasy Use			
Larger preferred dose	increased incidence of having been unconscious during or after drug use	not stated	Measham, Aldridge & Parker 2001
Larger preferred dose	increased incidence of vomiting during or after drug use	not stated	Measham, Aldridge & Parker 2001
Larger preferred dose	increased negative psychological effects during or after drugs	correlation, $r = 1.6$, $P < 0.05$	Measham, Aldridge & Parker 2001
Larger dose typically used	increased physical side effects	multiple linear regression* $\beta = 0.52$, $P < 0.01$	Topp et al. 1999
Significant tolerance to Ecstasy	increased Ecstasy-related problems (occupational, social, financial, and legal)	multiple linear regression*** $\beta = 0.69$, $P < 0.001$	Topp et al. 1999
Frequency of recent Ecstasy use	increased Ecstasy-related problems (occupational, social, financial, and legal)	multiple linear regression*** $\beta = 0.01$, $P < 0.01$	Topp et al. 1999
Bingeing	increased health problems	not stated	van de Wijngaart et al. 1999
Bingeing	increased incidence of self-defined depression	not stated	Hammersley, Khan & Ditton 2002
Having binged	increased Ecstasy-related financial problems	$\chi^2_1 = 16.2$; $P < 0.001$	Topp et al. 1999
Having binged	increased Ecstasy-related occupational problems	$\chi^2_1 = 7.1$; $P < 0.01$	Topp et al. 1999
Having binged	increased Ecstasy-related relationship problems	$\chi^2_1 = 19.1$; $P < 0.001$	Topp et al. 1999
Having binged	increased physical side effects	$t_{344} = -5.3$, $P < 0.001$	Topp et al. 1999
Having binged	increased psychological side effects	$t_{319} = 3.6$, $P < 0.001$	Topp et al. 1999
Recent bingeing	increased physical side effects	multiple linear regression* $\beta = 1.4$, $P < 0.005$	Topp et al. 1999
Recent bingeing	increased Ecstasy-related problems (occupational, social, financial, and legal)	multiple linear regression*** $\beta = 0.25$, $P < 0.05$	Topp et al. 1999
Gender			
Being female	increased acute hallucinogen-like effects after MDMA	Spearmen's rank order correlation $r = 0.68$, $P < 0.001$	Liechti, Gamma & Vollenweider 2001
Being female	dose-dependent anxiety (not seen in men)	Spearmen's rank order correlation $r = 0.5$, $P < 0.03$	Liechti, Gamma & Vollenweider 2001
Being female	increased acute side effects	main effect of dose x gender in ANOVA**** $F(1, 72) = 4.89$, $P < 0.05$	Liechti, Gamma & Vollenweider 2001
Being female	increased sub-acute side effects	main effect of dose x gender in ANOVA**** $F(1, 72) = 3.59$, $P < 0.05$	Liechti, Gamma & Vollenweider 2001
Being female	increased physical side effects	multiple linear regression* $\beta = 1.6$, $P < 0.001$	Topp et al. 1999
Being female	increased physical side effects	$t_{320} = -4.0$, $P < 0.001$	Topp et al. 1999
Being female	increased psychological side effects	multiple linear regression** $\beta = 0.91$, $P < 0.001$	Topp et al. 1999
Being female	increased psychological side effects	$t_{326} = -3.3$, $P < 0.05$	Topp et al. 1999
Being female	increased work or study problems	$\chi^2_1 = 9.0$ $P < 0.01$	Topp et al. 1999
Being female	increased frequency of illness at or after parties	not stated	van de Wijngaart et al. 1999
Being male	increased systolic blood pressure changes	main effect of dose x gender ANOVA**** $F(1, 72) = 4.49$, $P < 0.05$	Liechti, Gamma & Vollenweider 2001

TABLE 1 *(Continued)*

Risk Factor	Associated Event	Statistical Test	Reference
Age			
Being younger	increased physical side effects	multiple linear regression* $\beta= -0.20$, $P < 0.001$	Topp et al. 1999
Being younger	increased Ecstasy-related problems (occupational, social, financial, and legal)	multiple linear regression	Topp et al. 1999
Being younger	increased negative physical experiences	correlation, $r = -0.192$	Measham, Aldridge & Parker 2001
Being younger	increased negative psychological experiences	correlation, $r = -0.115$	Measham, Aldridge & Parker 2001
Being younger	decreased strategies used to reduce adverse drug effects	correlation, $r = 0.12$, $P < 0.05$	Measham, Aldridge & Parker 2001
Younger age of initiating Ecstasy use	increased negative physical and psychological effects use	not stated	Measham, Aldridge & Parker 2001
Duration of Drug Use			
Shorter duration of Ecstasy or amphetamine use	increased health problems	not stated	van de Wijngaart et al. 1999
Shorter duration of Ecstasy or amphetamine use	increased frequency of feeling sick at parties	not stated	van de Wijngaart et al. 1999
Shorter duration of Ecstasy or amphetamine use	increased utilization of first-aid areas	not stated	van de Wijngaart et al. 1999
Polydrug Use			
More extensive recent polydrug use	increased psychological side effects	multiple linear regression** $\beta = 0.15$, $P < 0.05$	Topp et al. 1999
Number of dance drugs self-identified user of	increased reported duration of recovery time	correlation, $r = 0.149$, $P < 0.01$	Measham, Aldridge & Parker 2001
Number of drugs self-identified user of	reported duration of recovery time	correlation, $r = 0.173$, $P < 0.1$	Measham, Aldridge & Parker 2001
Number of drugs typically used when recovering from Ecstasy	increased physical side effects	multiple linear regression * $\beta = 0.88$, $P < 0.001$	Topp et al. 1999
Number of drugs typically used when recovering from Ecstasy	increased psychological side effects	multiple linear regression** $\beta = 0.41$, $P < 0.001$	Topp et al. 1999
Number of drugs used	increased negative physical symptoms	correlation, $r = 0.267$, $P < 0.001$	Measham, Aldridge & Parker 2001
Number of drugs used	increased negative psychological symptoms	correlation, $r = 0.233$, $P < 0.001$	Measham, Aldridge & Parker 2001
Other Risk Factors			
Not having a regular and reliable dealer	increased health problems	not stated	van de Wijngaart et al. 1999
Not having a regular and reliable dealer	increased frequency of illness at parties	not stated	van de Wijngaart et al. 1999
Not having a regular and reliable dealer	increased frequency of visits to first-aid areas	not stated	van de Wijngaart et al. 1999
Attaching greater importance to clubbing	increased reported duration of recovery time	correlation, $r = 0.157$, $P < 0.01$	Measham, Aldridge & Parker 2001
Unemployment	increased physical side effects	multiple linear regression* $\beta = -1.2$, $P < 0.05$	Topp et al. 1999
Self-reported risk-taking at parties	increased visits to first-aid areas	not stated	van de Wijngaart et al. 1999
Self-reported risk-taking at parties	increased problems after a party	not stated	van de Wijngaart et al. 1999

*Final model predicting physical side effects was significant ($F_{6309} = 20.0$, $P < 0.201$), accounting for 29% of variance.

**Final model predicting psychological side effects was significant ($F_{4315} = 14.9$, $P < 0.001$), accounting for 16% of variance.

***Final model predicting number of Ecstasy-related problems (occupational, social, financial, and legal) was significant ($F_{4315} = 30.8$, $P < 0.001$), accounting for 28% of variance.

****2x2 analyses of variance (drug condition as within-subjects factor and gender as between-subjects factor) and Tukey's post hoc tests performed on significant effects.

neurotoxicity. In contrast to rare serious adverse events, risk factors for these common problems can be identified. In contrast to possible chronic neurotoxicity, there are indications that the more common problems cause many users to attempt to modify their behaviors to reduce the effects. This suggests that harm reduction programs could focus on reducing common Ecstasy-related problems, with particular emphasis on the roles of dose and "bingeing" in increasing these problems. Among other efforts, harm reduction programs could inform users, particularly new ones, about common Ecstasy-related symptoms so that symptoms can be recognized as drug-related when they occur. Symptoms of greater than minor severity could be presented as indicators of possible problem drug use, encouraging users to reconsider their relationships to Ecstasy. Similarly, users could be encouraged to be vigilant for loss of control and other indicators of abuse or dependence. If dose escalation and binge use can be avoided, there may be additional benefits beyond reducing common Ecstasy-related problems. Because animal studies indicate that serotonergic neurotoxicity is dose-dependent, reducing extent of Ecstasy use may also reduce neurotoxicity. It is also plausible that rare serious adverse events would be reduced.

CONCLUDING COMMENTS

The author must confess to a certain amount of sheepishness about the relatively simple recommendations in this article. Concluding that decreased Ecstasy use may lead to decreased Ecstasy-related problems is not particularly original. It is hoped that the details of this discussion may be more useful than this conclusion. This article discusses the lack of clear evidence for several hypothesized risk factors for Ecstasy-related serious adverse events. Based on this and other points, it has attempted to provide evidence that a preventative program focused on reducing "binge" Ecstasy use and other risk factors for common problems might be more useful than directly attempting to decrease rare serious adverse events or subtle neurotoxicity.

The specifics of such a program remain to be determined. It is possible that different messages should be tailored to specific subgroups of Ecstasy users, such as novice users or problem users. Measham, Aldridge and Parker (2001) have suggested that messages might also be tailored for the day of the week. Because much Ecstasy use occurs on weekends, information received on Friday afternoon (shortly before Ecstasy use) might be received differently than at a dance event (during Ecstasy intoxication) or Monday morning (during recovery from Ecstasy use). Time-specific messages could be implemented with modest expense using email and Web sites. Most importantly, preventative programs directed at Ecstasy users should be constructed with a focus on outcome measures that might be used to evaluate and guide the development of the programs.

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